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ORIGINAL ARTICLE

Factors associated with hematopoietic cell transplantation (HCT) among patients in a population-based study of myelodysplastic syndrome (MDS) in Minnesota

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Abstract Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by dysplastic changes in the bone marrow, ineffective erythropoiesis, and an increased risk of developing acute myeloid leukemia. Treatment planning for patients with MDS is a complex process, and we sought to better characterize hematopoietic cell transplantation (HCT) outcomes and the factors that play into decision-making regarding referral of adults with MDS for definitive therapy with HCT. Patients enrolled in a population-based study of MDS between April 2010 and January 2013 who underwent HCT within the first year after enrollment were included in this analysis. Age- and risk-matched MDS patient controls also enrolled during that time period were used as a comparison. Survival was significantly better in the HCT group (48 vs. 21 %, log-rank p value 0.009). Non-HCT patients were more likely to have comorbidities, and HCT patients were more likely to have a college degree and an income >$80,000. All three of these variables were independently associated with HCT, but none impacted survival. Patients with MDS in our study who underwent HCT had better survival than a comparable group of patients who did not undergo HCT. With refined treatment techniques, more patients may be able to be considered for this therapy. More work needs to be done to determine why education and income appear to impact the decision to pursue HCT, but these factors may impact referral to an academic center where aggressive therapy like HCT is more likely to be considered.

Keywords MDS · Myelodysplastic syndrome · Hematopoietic cell transplantation · Epidemiology

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Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by dysplastic changes in the bone marrow, ineffective erythropoiesis, and an increased risk of developing acute myeloid leukemia [1, 2]. MDS is generally a disease of the elderly with a median age at diagnosis of 65–70 years [3]. MDS occurs in 3–4 individuals per 100,000 in the US population [4], although recent evidence suggests that the incidence is much higher [5]. The prevalence of MDS increases with age and males are more commonly affected than females [4]. MDS is a heterogeneous disorder and classification schemes have evolved over the years. An updated World Health Organization (WHO) system was recently developed to more clearly define pathologic criteria [6]. Prognosis of MDS varies greatly depending on a multitude of patient- and disease-specific factors. Much work has been done in the development of scoring systems that aid prognostication and

treatment planning. The most widely used risk stratification systems include the International Prognostic Scoring System (IPSS), the Revised IPSS (IPSS-R), and the WHO Prognostic Scoring System (WPSS) [7–10].

Treatment strategies for MDS have evolved over the years. Supportive care measures, including transfusions and growth factors, can be used to ameliorate symptoms of cytopenias in low-risk MDS while aggressive chemotherapy is used to treat more advanced MDS, but hematopoietic cell transplantation (HCT) is the only curative option. Recently, hypomethylating agents including decitabine and azacytidine have been increasingly used. These agents can alter the disease course, improve survival, and in some cases serve as a bridge to HCT [11–15]. Choice of a treatment strategy depends on a number of factors, but most employ a risk-based treatment approach based on the IPSS risk stratification. Survival in patients with untreated intermediate 2 or high-risk disease is generally less than a year, so modifying the disease course and avoiding progression to acute leukemia are often the goals. Aggressive treatment including hypomethylating agents and HCT are considered in these patients. In low- or intermediate-1-risk disease, survival is longer so a less aggressive approach to maintain quality of life is generally utilized [2, 3]. Given that MDS is most often a disease of the elderly, other factors that need to be taken into consideration include age at diagnosis, functional status, and comorbidities. Other factors may play into decision-making as well but are not easy to discern or quantify.

Deciding on a treatment plan for patients with MDS is a complex process. With improved outcomes after HCT and the increased utilization of reduced-intensity conditioning regimens, we sought to better characterize the factors that play into decision-making regarding referral of adults with MDS for definitive therapy with HCT by reporting the outcomes of patients enrolled in a Minnesota population-based study who have undergone HCT and comparing them with adults with MDS who did not receive HCT and who are of similar age and disease risk.

Materials and methods

All procedures followed were in accordance with the ethical standards of the institutional review board and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients included in the study.

Study population and design

Adults in Minnesota with Myelodysplastic Syndromes (AIMMS) is a statewide prospective population-based study conducted by the University of Minnesota (UMN), Mayo Clinic, and Minnesota Department of Health. In April 2010,

the Minnesota Cancer Surveillance System (MCSS) began rapid case ascertainment of all newly diagnosed adult cases (ages 20+years) of MDS. Following physician approval, patients were contacted for invitation to enroll. Sixty-five percent of identified cases have been enrolled. An extensive questionnaire to gather epidemiologic data was completed by each participant at study entry. Central medical review, consisting of independent pathology review of bone marrow and peripheral blood samples by two hematopathologists along with independent cytogenetic interpretation by a cytogeneticist, was then performed starting at MDS diagnosis. Reports were integrated, with discrepancies in WHO classification requiring collaboration for a unifying subtype according to the 2008 revised criteria [6]. Cases without diagnostic verification were excluded.

The pathologic review was coupled with a chart review by an oncologist to assign prognostic risk scores (IPSS and/or IPSS-R) [7, 8]. Scores were calculated independently for each patient, and lack of necessary cytogenetic and hematologic data to calculate risk scores resulted in case exclusion. Treatment exposures and responses were abstracted, including relevant exposures prior to formal diagnosis when available. Per the AIMMS study design, enrollment of cases diagnosed before November 2014 will continue into early 2015, with annual clinical review of all patient cases planned for 3 years following their initial enrollment.

Patients enrolled on AIMMS between April 2010 and January 2013 who had at least 1 year of prospective follow-up were included in this analysis, which consisted of two parts. The first was a description of characteristics and outcomes of patients enrolled during this time period who underwent HCT. The second was a comparison of the patients who underwent HCT to age- and risk-matched MDS controls enrolled on AIMMS during the same time period who did not undergo HCT. Additional medical record review for all patients in this analysis included consideration of HCT, comorbidities, HCT-specific data, and HCT outcomes. Academic centers were defined as the UMN and Mayo Clinic, with all other sites designated as community-based practices. Comorbidities were gathered from the questionnaire and medical records. In an attempt to categorize them with regard to severity, we utilized the HCT-CI weighing and scoring system. A score of 0 was considered low risk, 1–2 intermediate risk, and 3+ high risk [16].

Statistical methods

Contingency table methods were used for comparison of categorical data. Kaplan-Meier survival curves were used to compare differences in survival between HCT and non-HCT patients. We used Cox proportional hazards regression to compute crude and adjusted hazard ratios (HR) and 95 % confidence intervals (CI) to identify predictors of survival

among cases who underwent HCT and between HCT and non-HCT cases. Age at diagnosis (continuous), sex, WHO MDS classification (RAEB-1, RAEB-2, RCMD, tMDS, other), IPSS-R (low or intermediate, high, very high), WPSS (very low/low/intermediate, high, very high), number of comorbidities (0–1, 2–3, 4+), comorbidity risk score (low risk, intermediate risk, high risk), education (≤high school, some post high school, college graduate), and income (≤$40,000, $40,000–80,000, >$80,000) were evaluated as potential confounders. Variables were included in the final model if they changed the magnitude of the HR for HCT>10 %. All statistical analyses were conducted using SAS (Version 9.3, Cary, NC) and all reported p values are two-sided.

Results

Patient characteristics

A total of 342 patients were enrolled on AIMMS between April 2010 and January 2013. Of those, 33 (9.6 %) underwent HCT in the first year after enrollment. Thirty-two patients of similar age and disease risk enrolled during the same time period and not undergoing HCT were identified to serve as a comparison to the HCT patients. In these control patients, the reasons for not pursuing HCT included comorbidities ($n=8$), progressive disease ($n=8$), patient refusal ($n=3$), financial reasons and lack of a caregiver ($n=1$), and no consideration of HCT documented ($n=12$). Characteristics of the 65 patients analyzed are outlined in Table 1. The median age at diagnosis of MDS was 59 years (range 25–70) in the HCT group and 63 years (range 51–75) in the non-HCT group ($p=0.07$). There were no significant differences in MDS severity between the HCT and non-HCT groups based on WHO classification, IPSS-R risk category, or WPSS risk category. Sex, marital status, and ethnicity were similar. The ethnic background of the majority of patients (non-Hispanic white) reflects the population in Minnesota and those most at risk of MDS.

HCT characteristics and outcomes

The cited reasons for pursuing HCT were disease risk and age. The median time from diagnosis to HCT was 199 days (range 36–778). Most patients received some active therapy prior to HCT (standard cytotoxic chemotherapy only [$n=11$], hypomethylating agent only [$n=5$], hypomethylating agent and cytotoxic chemotherapy [$n=13$]). Nineteen patients received their HCT at the UMN and 14 at the Mayo Clinic. Donor source was unrelated in 61 %. Graft source was peripheral blood stem cells in 61 %, double umbilical cord blood in 33 %, and bone marrow in 6 %. The majority received reduced-intensity conditioning (85 %) and cyclosporine-based graft versus host disease (GVHD) prophylaxis (72 %).

Thirty-two patients achieved neutrophil engraftment at a median of 14 days (range 6–25). GVHD occurred in 36 % of patients. The most common HCT-related complication was infection (viral, bacterial, or fungal). Median follow-up is 732 days (range 25–1506). Relapse occurred in 24 % of patients and overall survival was 48 %. Though not significant, IPSS-R risk classification appeared to predict survival among HCT patients (Table 2). Those patients with high or very high risk classification had a twofold (HR 2.34, CI 0.47–11.8, $p=0.30$) and threefold (HR 3.30, CI 0.84–12.9, $p=0.09$) increased risk of death, respectively. Importantly, the comorbidity score did not negatively impact survival. Sex, donor source (unrelated vs. sibling), graft source (bone marrow vs. peripheral blood stem cells vs. double umbilical cord blood), conditioning intensity, and time to engraftment also did not impact survival.

Comparison of HCT and non-HCT patients

Table 3 shows a comparison between the HCT and non-HCT groups. As noted previously, there was no significant difference in MDS risk classification between the two groups (see Table 1). Other disease characteristics were also similar between the groups. Location of disease diagnosis (urban vs. rural) was similar between the two groups, but there were more patients in the non-HCT group being treated exclusively in a community setting (38 vs. 6.1 %, $p=0.008$). More non-HCT patients received supportive care only (41 vs. 9.1 %, $p=0.007$). Non-HCT patients had a higher number of comorbidities ($p=0.0005$) and were more likely to have a high-risk comorbidity score ($p<0.0001$). HCT patients were more likely to have a college degree (61 vs. 26 %, $p=0.02$) and to have an income >$80,000 (44 vs. 13 %, $p=0.02$). There were no statistically significant associations between comorbidities and education level or income. When the number of comorbidities was included in an adjusted model with education and income, none of the variables was significantly associated with transplant although confidence intervals were wide. Cases with higher numbers of comorbidities were less likely to receive HCT (OR 0.23, 95 % CI 0.04–1.39 for 4+ comorbidities vs. 0–1 comorbidity), and those with higher education (OR=3.99, 95 % CI 0.40–40 for college graduate vs. less than college graduate) and income (OR=1.72, 95 % CI 0.25–12 for >$80,000 vs. ≤$40,000) were more likely to receive HCT.

Median time from diagnosis to death or last follow-up was 847 days (211–1628) in the HCT group and 398 days (range 92–1826) in the non-HCT group. Survival was significantly better in the HCT group (48 vs. 21 %, log-rank p value 0.009) (Fig. 1). The causes of death in the HCT group include recurrent MDS ($n=8$), infection ($n=3$), GVHD ($n=2$), post transplant lymphoproliferative disease ($n=1$), and recurrent

Table 1 Characteristics of the study population

	MDS HCT patients N (%)	MDS non-HCT patients N (%)	p value
Total	33	32	
Median age at diagnosis (range)	59 (25–70)	63 (51–75)	0.07
Sex			
Male	22 (67)	24 (75)	
Female	11 (33)	8 (25)	0.46
Race/ethnicity			
Non-Hispanic white	31 (94)	29 (91)	
Other	2 (6.1)	3 (9.4)	0.62
Marital status			
Married/living together	27 (82)	22 (69)	
Other	6 (18)	10 (31)	0.22
WHO classification			
Refractory thrombocytopenia	1 (3.0)	0	
RCMD	1 (3.0)	5 (16)	
RARS	0	2 (6.2)	
RAEB-1	6 (18)	6 (19)	
RAEB-2	16 (48)	8 (25)	
Therapy-related MDS	9 (27)	9 (28)	
Unclassifiable	0	2 (6.2)	0.12
IPSS-R			
Low or intermediate	13 (43)	9 (29)	
High	5 (17)	10 (32)	
Very high	12 (40)	12 (39)	0.30
Missing	3	1	
WPSS			
Very low, low, intermediate	3 (9.4)	5 (17)	
High	21 (66)	15 (51)	
Very high	8 (25)	9 (31)	0.54
Missing	1	3	

WHO World Health Organization, *RCMD* refractory cytopenia with multi-lineage dysplasia, *RAEB* refractory anemia with excess blasts, *IPSS-R* Revised International Prognostic Scoring System, *WPSS* WHO-based Prognostic Scoring System

osteosarcoma ($n=1$). The causes of death in the non-HCT group include progressive MDS ($n=16$), infection ($n=2$), pulmonary fibrosis ($n=1$), pulmonary hemorrhage ($n=1$), and unknown ($n=2$). In a univariate model, undergoing HCT had a positive impact on survival (HR 0.43, 95 % CI 0.22–0.83, $p=0.01$), while IPSS-R high (HR 6.06, 95 % CI 1.95–19, $p=0.002$) and very high risk (HR 8.75, 95 % CI 2.94–26.0, $p<0.0001$) classification had a negative impact on survival. The adjusted model showed similar outcomes with regard to HCT (HR 0.25, 95 % CI 0.09–0.75, $p=0.01$) and IPSS-R risk classification (IPSS-R high HR 5.99, 95 % CI 1.51–23.7, $p=0.01$; IPSS-R very high HR 11.1, 95 % CI 3.10–39.8, $p=0.0002$). Importantly, comorbidities did not appear to negatively impact survival in our cohort of patients. Age at diagnosis, education and income group also did not appear to impact survival (Table 4).

Discussion

Determining a treatment plan for patients with MDS is a complex process, and this analysis sought to investigate differences between patients who underwent HCT and those who did not. Age, disease risk, and performance status are historically the most important factors taken into consideration when determining a treatment plan. This case-control analysis revealed several other factors, some expected and some unexpected, that also appear to play into the decision of whether to offer curative therapy with HCT. Not surprisingly, the presence and severity of comorbidities impacted whether a patient received HCT. Interestingly though, neither number nor severity of comorbidities negatively impacted survival in multivariate analysis. Unexpectedly,

Table 2 Predictors of survival among HCT patients

	Crude HR (95 % CI)	*p* value
Age at diagnosis	1.00 (0.95–1.05)	0.99
Female sex	0.70 (0.22–2.22)	0.55
Time from diagnosis to transplant	1.00 (0.99–1.01)	0.82
Pre-transplant therapy		
Supportive care	1.22 (0.29–5.19)	0.79
Standard cytotoxic chemotherapy only	Ref	
Hypomethylating agent only	0.44 (0.05–3.81)	0.46
Standard cytotoxic chemotherapy+hypomethylating agent	1.35 (0.40–4.53)	0.62
Donor source		
Unrelated	Ref	
Sibling	0.61 (0.21–1.79)	0.37
Graft source		
Bone marrow	0.28 (0.03–2.73)	0.27
Peripheral blood stem cells	0.41 (0.14–1.21)	0.11
Double umbilical cord blood	Ref.	
Conditioning intensity		
Reduced intensity	Ref.	
Myeloablative	1.71 (0.53–5.56)	0.37
Time to engraftment	0.98 (0.89–1.08)	0.71
GVHD		
No	Ref	
Yes	2.23 (0.79–6.28)	0.13
Comorbidity risk score		
Low risk	Ref	
Intermediate risk	0.91 (0.27–3.05)	0.87
High risk	0.54 (0.12–2.46)	0.42
IPSS-R		
Low or intermediate	Ref	
High	2.34 (0.47–11.8)	0.30
Very high	3.30 (0.84–12.9)	0.09

education and income also seemed to play a role. Patients who underwent HCT had more education and a higher income than those who did not undergo HCT though again neither of these factors impacted overall survival.

When determining whether HCT is appropriate to offer patients with MDS, many factors are taken into consideration. Age, disease risk, and comorbidities are all easily explainable, but why education and income appear to play a role is not as clear. Comorbidities are often linked with socioeconomic status, which then could explain why less education and a lower income are associated with not receiving HCT. However, in our cohort of patients, comorbidities, education, and income were all independently predictive of HCT in a multivariate model. Race, which can be associated with education and income and can also be a factor in HCT decisions since unrelated donors are less readily available in minorities, was also examined and was not different between the groups.

A recent analysis from our population-based study of MDS showed that younger patients and those treated at academic centers received more aggressive treatment approaches, a trend that was consistent across all IPSS and IPSS-R risk categories [17]. Given this information, one hypothesis to potentially explain our finding that education and income impacts the decision to pursue HCT is that education and income affect referral to an academic center and subsequently the aggressiveness of treatment. While difficult to determine in our small cohort, we performed an association analysis which revealed that those with less education appeared to receive their therapy at a community center more often than those with more education. A similar association between treatment type and income and education was seen in the larger, unselected dataset used in the analysis by Pease et al., making unintentional selection bias due to small numbers less likely.

Referral to an academic center where HCT is performed is a critical step in the treatment decision-making process. If

**Table 3** Comparison of HCT and non-HCT patients

	MDS HCT patients	MDS non-HCT patients	p value
Vital status			
Alive	18 (55)	10 (31)	
Dead	15 (45)	22 (69)	0.06
Education			
≤High school graduate	3 (9.1)	7 (23)	
Some college	10 (30)	16 (52)	
College graduate	20 (61)	8 (26)	0.02
Income group			
≤$40,000	6 (19)	10 (32)	
>$40,000–$80,000	12 (38)	17 (55)	
>$80,000	14 (44)	4 (13)	0.02
Treatment location			
Community	2 (6.1)	12 (38)	
Community referred to academic	21 (64)	14 (44)	
Academic	10 (30)	6 (19)	0.008
Treatment at MDS diagnosis			
Standard chemotherapy	16 (48)	7 (22)	
Hypomethylating agent	14 (42)	12 (38)	
Supportive care	3 (9.1)	13 (41)	0.007
Location of residence at MDS diagnosis			
Rural	7 (21)	8 (25)	
Urban	26 (79)	24 (75)	0.71
Number of comorbidities			
0–1	13 (39)	6 (19)	
2–3	17 (52)	12 (38)	
4+	3 (9.1)	14 (44)	0.005
Comorbidity risk score			
Low risk (0)	7 (21)	3 (9.4)	
Intermediate risk (1–2)	16 (48)	2 (6.3)	
High risk (3+)	10 (30)	27 (84)	<0.0001

education and income impact the likelihood of referral to an academic center and those who are treated at an academic center are more likely to receive aggressive treatment approaches, then it makes sense that those with less education and income are less likely to undergo curative therapy with HCT. It is impossible for us to determine why referrals occurred less often in these patients in our cohort, but potential reasons include inadequate insurance coverage and a lack of resources (e.g., ability to get time off work needed to undergo HCT).

Outcomes in our patients who underwent HCT are similar to other published reports showing an overall survival of 30–50 % [3, 18, 19]. A recent Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of MDS patients undergoing HCT at US transplant centers revealed a 2-year overall survival of 47 and 44 % for transplants occurring between 2008–2010 and 2004–2007, respectively. This is

a significant improvement when compared to patients transplanted prior to 2000 when the 2-year overall survival was 34–39 % [20]. Several factors are likely responsible for this improvement including better human leukocyte antigen matching and better management of HCT-related complications [21]. The only predictor of survival in HCT patients in our study appeared to be IPSS-R risk classification. This is not surprising as it is well described that patients with higher risk disease do less well with any therapy, including HCT [22, 23]. Even though the presence and severity of comorbidities affected whether or not HCT was offered to patients in this cohort, in contrast to other published reports [24, 25], comorbidities did not negatively impact survival. It is likely that we were unable to completely assess comorbidities in our cohort leading to an inaccurate assessment of their impact on survival. Notably, survival in our cohort is significantly better in patients who underwent HCT despite similar age and disease

Fig. 1 Probability of survival. Kaplan-Meier survival curves comparing transplanted and non-transplanted patients. + denotes censored. Log-rank *p* value= 0.009
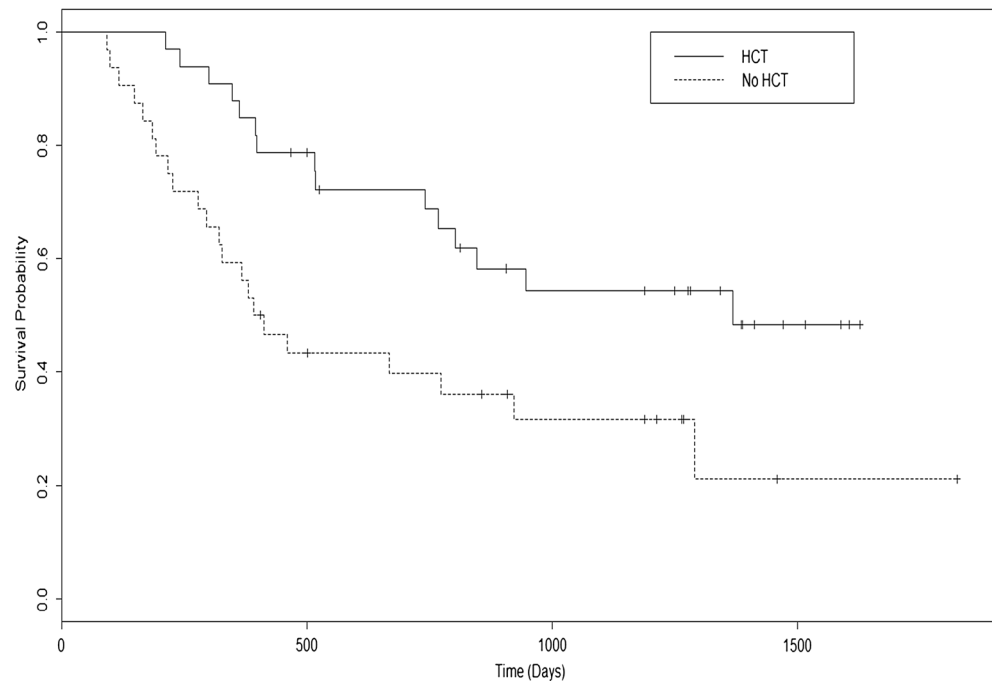
risk (48 vs. 21 %). This positive impact on survival remains even in multivariate analysis. Longer follow-up is needed to determine if this survival advantage persists.

Our analysis is unique in that it reports data from a population-based study of MDS that employs a rigorous central pathologic review process and direct chart review

Table 4 Predictors of survival among all patients

	Crude HR (95 % CI)	*p* value	Adjusted[a] HR (95 % CI)	*p* value
HCT	0.43 (0.22–0.83)	0.01	0.25 (0.09–0.75)	0.01
Age at diagnosis	0.99 (0.96–1.02)	0.47	1.00 (0.93–1.07)	0.96
Female sex	0.58 (0.26–1.27)	0.17	0.61 (0.18–2.09)	0.43
IPSS-R				
Low or intermediate	Ref		Ref	
High	6.06 (1.95–18.8)	0.002	5.99 (1.51–23.7)	0.01
Very high	8.75 (2.94–26.0)	<0.0001	11.1 (3.10–39.8)	0.0002
Number of comorbidities				
0–1	Ref			
2–3	1.25 (0.55–2.82)	0.60		
4+	1.88 (0.79–4.48)	0.15		
Comorbidity score				
Low risk (0)	Ref		Ref	
Intermediate risk (1–2)	1.12 (0.46–2.75)	0.80	0.89 (0.24–3.34)	0.87
High risk (3+)	0.56 (0.19–1.63)	0.29	0.68 (0.17–2.77)	0.59
Education				
≤High school grad	Ref		Ref	
Some post HS	0.81 (0.31–2.13)	0.67	1.07 (0.31–3.75)	0.92
College grad	1.04 (0.41–2.65)	0.93	1.87 (0.54–6.44)	0.32
Income group				
≤$40,000	Ref		Ref	
>$40,000–$80,000	0.78 (0.36–1.67)	0.52	1.54 (0.56–4.23)	0.40
>$80,000	0.70 (0.29–1.69)	0.42	1.76 (0.52–5.99)	0.36

[a] Adjusted for HCT, age at diagnosis, sex, IPSS-R, and comorbidity score

providing a high degree of diagnostic certainty, but it is limited by small numbers. In addition, despite the direct chart review process, we were only able to account for comorbidities and factors that were overtly written in the available medical records and those that were reported by the patient in their initial questionnaire. This reporting and recall bias likely results in an underestimate of the incidence and severity of comorbidities in the patient population, but should affect both the HCT and non-HCT groups equally.

In our study period, 65 % of those diagnosed with MDS in Minnesota were captured in AIMMS and 56 % had complete pathology review. Reasons for not enrolling include the following: patient deceased before contact ($n=83$), language ineligible ($n=2$), lost to follow-up ($n=16$), refusal ($n=70$), and non-participating site ($n=1$). Forty-three patients are still in process for study enrollment.

Patients with MDS in our study who underwent HCT had better survival than a comparable group of patients who did not undergo HCT. With refined treatment techniques, including hypomethylating agents and reduced-intensity conditioning, more patients may be able to be considered for this therapy. More work needs to be done to determine why education and income appear to impact the decision to pursue HCT, but these factors may impact referral to an academic center where aggressive therapy like HCT is more likely to be considered.

Conflict of interest The authors declare that they have no competing interests.

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